Mathematical Modeling of Enteric Glia-Derived Immune-Metabolic Crosstalk Reveals Synergistic Strategies to Overcome PRDM9- Mediated Ferroptosis Resistance in Glioblastoma

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Glioblastoma (GBM) is the most aggressive type of primary brain tumor, with limited response to standard temozolomide (TMZ) therapy due to resistance. Thus, the search for alternative treatment methods becomes meaningful. Recent studies reveals that the germline gene PRDM9 helps tumors become drug-tolerant but its role outside the germline in GBM remains unexplored. This study presents a novel multi-scale mathematical model to investigate how enteric glia–mediated interferon-gamma (IFN-?) modulates PRDM9-driven cholesterol metabolism and BKCa channel activity, which in turn impacts ferroptosis sensitivity and treatment response. A system of nine ordinary differential equations (ODEs) was developed to integrate tumor growth, immune dynamics, and a resistance module. The model introduces a quantitative Ferroptosis Resistance Score (FRS) to capture ferroptosis sensitization and resistance across 8 treatment conditions. The results show that using TMZ and IFN-? together is almost as effective (33.5%) as triple therapy (34.11%), and it lowers the FRS by 71% ($p<0.001$). IFN-? mainly boosts short-term ferroptosis sensitivity, while blocking BKCa channels with paxilline may act as a long-term resistance disrupting agent. Bliss independence analysis shows that the dual combination works synergistic together, but triple combination acts slightly antagonistic due to pathway redundancy. Sensitivity analysis found that parameters related to ferroptosis and IFN-? are the main drivers of treatment response. This work introduces a novel ferroptosis resistance axis in GBM and proposes a gut–brain axis–mediated therapeutic strategy. It further provides a framework for optimizing combination therapies and highlights experimentally testable targets for overcoming resistance.

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